SMOKING CESSATION: EFFECTS ON SYMPTOMS, SPIROMETRY AND FUTURE TRENDS IN COPD

ii7

N B Pride

Introductory article

Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study

P D Scanlon, J E Connett, L A Waller, M D Altose, W C Bailey, A S Buist

*Previous studies of lung function in relation to smoking cessation have not adequately quantified the long-term benefit of smoking cessation, nor established the predictive value of characteristics such as airway hyperresponsiveness. In a prospective randomized clinical trial at 10 North American medical centers, we studied 3926 smokers with mild-to-moderate airway obstruction (3818 with analyzable results; mean age at entry, 48.5 yr; 36% women) randomized to one of two smoking cessation groups or to a nonintervention group. We measured lung function annually for 5 years. Participants who stopped smoking experienced an improvement in FEV_1 in the year after quitting (an average of 47 ml or 2%). The subsequent rate of decline in FEV_1 among sustained quitters was half the rate among continuing smokers, 31 ± 48 versus 62 ± 55 ml (mean $\pm$ SD), comparable to that of never-smokers. Predictors of change in lung function included responsiveness to beta-agonist, baseline FEV_1, methacholine reactivity, age, sex, race, and baseline smoking rate. Respiratory symptoms were not predictive of changes in lung function. Smokers with airflow obstruction benefit from quitting despite previous heavy smoking, advanced age, poor baseline lung function, or airway hyperresponsiveness. (**Am J Respir Crit Care Med** 2000;161(2 Pt 1):381–90)*

This review discusses the expected results of sustained quitting smoking on subsequent lung disease, particularly chronic obstructive pulmonary disease (COPD), rather than the approaches which health professionals can use to aid an individual to become an ex-smoker. The latter topic was reviewed by Campbell in last year's *Thorax Year in Review*[1] and updated guidelines have since been published in *Thorax*.[2]

Health care workers remark regularly on the low rates of success in most short term studies of smoking cessation; when higher rates of sustained quitting are obtained—such as the exceptional 5 year rate of 22% in the Lung Health Study[3] or the creditable figure of 22% at 1 year in trials of bupropion and/or nicotine patches[4]—the support given to individuals in these studies is far beyond that which could be committed on a wider basis. These results would certainly be troubling if quitting smoking usually depended on a single attempt with specific medical assistance or other formal support, but more than 90% of successful quitters in the USA do so without any such help,[5] many making repeated attempts over a long period to quit before sustained success is achieved. In countries such as the UK and USA where the smoking epidemic has passed its peak, the quit ratio (ex-smokers as a percentage of ever-regular smokers) has risen year by year; in the UK it is 47% in men and 44% in women and has even reached 70% in men over 65 in whom the rate is admittedly enhanced by attrition suffered by the smoking men.[6 7] The result is that up to one third of the UK adult population over 30 years are ex-smokers and are disproportionately represented in the older age groups.[6] As discussed in an important paper published last year by Peto *et al*,[7] the benefits for lung cancer incidence from this have been seen for many years in UK men and there are indications that the epidemic in women may be reaching its peak. Similar reductions in lung cancer death risks have been reported in the USA.[8 9] Can we expect such encouraging results in another disease strongly related to smoking—namely, COPD?

Department of Thoracic Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London SW3 6LY, UK
N B Pride

Correspondence to: Professor N B Pride

n.pride@ic.ac.uk

▶ **EFFECTS ON LUNG FUNCTION AND SYMPTOMS**

The classic studies of Fletcher and colleagues in West London in the 1960s showed that the annual decline of forced expiratory volume in 1 second (FEV_1) in ex-smokers on average approached the levels in healthy never smokers,[10] and this was confirmed subsequently in a large
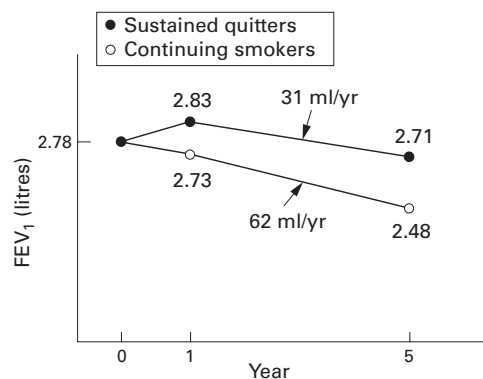
Figure 1 Scheme of mean changes in FEV$_1$ in continuing smokers and sustained quitters in the Lung Health Study (data extracted from Scanlon et al[11]).

number of longitudinal studies. However, the landmark study which confirmed these results was the Lung Health Study in North America, the first results of which were reported in 1994.[3] This study was notable for the large numbers of heavy cigarette smokers studied, the success in achieving validated, sustained cessation in 559 of these individuals, and randomisation of the application of the smoking cessation programme. The results relating to smoking cessation have been expanded in two further recently published papers dealing with changes in lung function[11] and symptoms,[12] the former being the introductory article reviewed here. Re-analysis of the effects on lung function confirms that there is a small mean improvement of 47 ml in post-bronchodilator FEV$_1$ in the first year after quitting (which, of course, would not be measurable in an individual smoker) and that subsequently the mean annual decline in sustained quitters was 31 ml/year, similar to that in healthy never smokers in many studies and exactly half that seen in continuing smokers (62 ml/year). Hence, over the 5 year period of the study the mean decrement in FEV$_1$ was 77 ml in quitters compared with 296 ml in continuing smokers (fig 1). Many factors (such as daily cigarette consumption, baseline lung function, age, and sex) were examined to see whether they influenced the effect on the spirometric test results, but all were negative. These results provide an extremely strong basis for predicting the effects of quitting on FEV$_1$. Although there is a small benefit in the first year after quitting, the major effect is in slowing future decline. Indeed, these results provide the "gold" standard for other interventions which aim to attenuate the decline in FEV$_1$—a target not yet achieved by any other preventive treatment. A separate analysis[12] was made of the effects of quitting on reducing symptoms. Again, many earlier smaller studies had recorded these changes. The results confirm the remarkably swift and sustained reduction in symptoms of cough, phlegm, and wheeze in smokers who were able to quit. For instance, more than 80% of sustained quitters who had chronic cough at baseline when still smoking reported that they no longer had cough 1 year later. Similar reductions were noted in phlegm production and wheezing. Reductions in symptoms were sustained throughout the 5 years of follow up and very few sustained quitters reported these symptoms newly developing during that period. These findings are extremely encouraging for patients who have to be forewarned that changes in dyspnoea and lung function are not going to be so obvious.

The mean results from the Lung Health Study were obtained in middle aged subjects (mean age 48 years) with mild to moderate impairment of FEV$_1$ (mean 78% predicted

after bronchodilators), most of whom were not "patients". Because first clinical presentation is often at an older age and with greater spirometric impairment, an important question is: "Does similar slowing in the annual decline in FEV$_1$ occur when the disease is more advanced?"

There is almost no information on this question. However, as about half of the participants in the ISOLDE trial of inhaled steroids in patients with COPD were ex-smokers and had a mean post-bronchodilator FEV$_1$ of only 50% predicted,[13] some information may be forthcoming. Certainly, the same size of benefit cannot be assumed; indeed, many clinicians believe that, once significant disease has developed, it can progress after the original initiating process has been removed. A mechanical hypothesis can be constructed where breaks in the alveolar walls and uneven distension of alveoli lead to abnormal localisation of stress points which promote further alveolar destruction. Furthermore, several cross sectional studies of airway biopsies have failed to find differences between airway inflammatory changes in smokers and ex-smokers of considerable duration,[14–16] although in two of these studies[15 16] persistent chronic bronchitis was present in most subjects, contrasting with its usual resolution in sustained quitters in the Lung Health Study.[12] Because airway inflammation is present in all smokers and differs in intensity rather than in additional specific features in those with developed COPD, detailed quantification of changes is required, preferably in prolonged longitudinal studies in quitters. A more practical method for studying sequential changes may be by following surrogate markers of inflammation in induced sputum or exhalate.

The standard deviation of the annual rates of decline in FEV$_1$ in the Lung Health Study (48 ml/year in quitters and 55 ml/year in continuing smokers) indicates that, even over 5 years of follow up, confidence in a value for the annual decline in an individual is low and that there is plenty of room, even in this moderately obstructed group, for individual ex-smokers to show continuing accelerated decline. Nevertheless, the overall message remains that, on average, the decline in FEV$_1$ reverts to values similar to those in healthy never smokers. Reduction in cough and sputum should improve health status and reduce the subsequent rate of exacerbations which are related to the presence of persistent cough[10] and the severity of impairment of lung function.[14] Because any previous smoking related impairment in FEV$_1$ persists in quitters, smoking related airflow obstruction without accompanying cough is likely to increase in the community at large, adding to the considerable prevalence in continuing smokers originally noted in Fletcher's study.[10] Recent evidence from the Lung Health Study and the large trials of inhaled glucocorticosteroids suggests that chronic bronchitis was only present in about half the smokers recruited with airflow obstruction.[3 12 17–19] Cough and phlegm production are easily detected in surveys, provide the most obvious hints to smokers that their lungs are affected, and also help to identify smokers at an increased risk of COPD and lung cancer.[20] However, because obstruction without chronic cough is common and spirometric impairment in the population is often unidentified by both the sufferer and the health care system,[21] the presence of cough and/or phlegm cannot be a prerequisite for proceeding to spirometric testing in the community any more than symptoms alone can be used to detect high blood pressure or diabetes.

Learning points

► Quitting smoking when impairment of FEV_1 is moderate leads to a mean annual decline in FEV_1 similar to that of healthy never smokers and a reduction in cough, phlegm and wheeze in most individuals within the first year.

► When lung function is more severely impaired, the effects of smoking cessation on symptoms and on the subsequent decline in FEV_1 are not known.

► The prevalence of smoking is greatest and cessation least in deprived individuals who are at most risk of COPD.

► The large survival benefits for total, cardiovascular, and lung cancer mortality make smoking cessation the most important treatment for all patients with COPD.

► Because of its long preclinical course, quitting early is needed to obtain reductions in morbidity and mortality due to COPD.

ii9

Long term effects of quitting on trends in COPD

There is an inevitable gap between the available relatively short term studies over 3–7 years of mildly affected subjects in middle age (although the Lung Health Study is continuing) and assessment of the effects of the increased numbers of ex-smokers and reduced numbers of current smokers on future trends in the UK. Long term data on the fate of ex-smokers have only become available in recent decades in countries where the peak of the male smoking epidemic was 20–30 years ago. The Cancer Prevention Study II of the American Cancer Society[8] and the 40 year follow up study in UK male doctors[22] both showed that death from COPD actually increased for the first 5–10 years after quitting, presumably reflecting the effects of late quitting when disease was already advanced. In both studies declines in lung cancer mortality were seen earlier after smoking cessation.[8 9 22] These two studies had no information on lung function.

A recent paper from Finland,[23] discussed in an editorial in *Thorax*,[24] examined FEV_1, smoking habit, and subsequent 30 year all-cause mortality in a cohort of men born between 1900 and 1919 who were first studied in 1959. Former smokers had a 6–7 year longer median survival time than continuing smokers due to reductions in both total and cardiovascular mortality. This benefit was somewhat greater in those with lowest initial FEV_1, confirming previous observations of the value of lung function tests in predicting subsequent mortality, especially that due to cardiovascular disease.[25 26] The number of deaths due to COPD was small and not decreased in former smokers. Because lung function inevitably declines with age in healthy subjects, even a decline at normal rates in ex-smokers who quit with an established impairment of lung function might delay rather than prevent death from COPD. Slower progression of disease might incur health care costs over a greater number of years in an individual and accentuate the existing trend for identification of disease and its mortality to be concentrated in the elderly.[27]

Continuing smoking in the presence of established COPD and progressive symptoms is sometimes regarded as indicating that patients with COPD are particularly addicted to nicotine. No support for this is given by the quit rates in the Lung Health Study, although in a recent trial of bupropion abstinence rates were lower in patients with more severe COPD.[28] Participants in formal studies may not be representative of patients with COPD in the community, and

there are other reasons for thinking that trends in COPD might be less striking than suggested by the percentage of ex-smokers in the population and the huge overall benefit of quitting on mortality rates. Firstly, quitters are concentrated in the more affluent sections of the population, yet COPD has a very strong relation to low socioeconomic status. This bias was present 50 years ago when smoking was relatively uniform through the male population, and is presumably being accentuated by the increasing socioeconomic bias of smoking habits in both men and women over the last 30 years.[6] The same trend applies to new smokers which shows little attenuation in the poorer or less educated section of the population in the UK or USA (70% of the male cohort born in the 1960s in the USA who did not complete high school took up smoking[29]). Secondly, at least in the UK, COPD is historically not so strongly related to smoking as lung cancer, which appears to have been uncommon before cigarette smoking was adopted during the first half of the 20th century. Considerable mortality from COPD was present in both men and women before cigarette smoking was introduced.[30] Even after World War II, deaths recorded from COPD in women were declining in 1950–70 at a time when smoking and lung cancer mortality were rising,[31] indicating the importance of other risk factors in the pathogenesis of COPD. The current smoking attributed risk in the UK for COPD, although about 80% in men and still increasing in women, is still not so high as for lung cancer.[32] The nature of these other risk factors and the reasons for their decline are speculative (in contrast to other countries, including the USA, death from COPD in UK men has been declining steadily for the last 30 years). Obvious candidates are environmental and domestic pollution, the latter perhaps being related to heating and cooking in confined spaces. Such factors could interact with entering adult life with relatively poorly developed lung function. Persistence of other risk factors is indicated by the finding that about 5% of the non-asthmatic, never smoking population have chronic bronchitis and/or abnormal spirometric parameters.[21 33] No doubt some of these have unrecognised bronchiectasis, cystic fibrosis, or a specific environmental exposure, but details on this sizeable proportion of the population are sparse.

To summarise, quitting smoking at any age is certainly the most important "treatment" for the patient with COPD, just as it is for the population at large, and health professionals have to be more pro-active in assisting this. Unless means of repairing and regenerating lung function are found, quitting

smoking in middle age, by attenuating symptoms and deterioration in lung function, is unlikely to be rivalled for COPD, let alone its benefits for the incidence of lung cancer, ischaemic heart disease, and many other conditions. However, the relation of smoking and quitting to COPD is not so clearly "present/absent" as with lung cancer with its depressingly high ability to kill most sufferers in a short time from diagnosis. Quitting smoking early in life is naturally important for maximum reductions in total mortality and mortality from lung cancer but, because of the long prodrome of clinical COPD (and the inevitable deterioration in lung function with age), it is probably even more important for COPD. In the meantime, we have to anticipate that downward trends in morbidity and mortality from COPD may be less than suggested by the overall success of the population in quitting smoking.

ii10

References

1 **Campbell IA**. Smoking cessation. *Thorax* 2000;**55**(Suppl 1):S28–31.

2 **West R**, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. *Thorax* 2000;**55**:987–99.

3 **Anthonisen NR**, Connett JE, Kiley JP, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline in FEV_1: the Lung Health Study. *JAMA* 1994;**272**:1497–505.

4 **Jorenby DE**, Leischow SJ, Nides A, *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;**340**:685–91.

5 **Fiore MC**, Novotny TE, Pierce JP, *et al.* Methods used to quit smoking in the United States. Do cessation programs help? *JAMA* 1990;**263**:2760–5.

6 **General Household Survey for Year 1998**. London: Stationery Office, 2000.

7 **Peto R**, Darby S, Deo H, *et al.* Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ* 2000;**321**:323–9.

8 **US Department of Health and Human Services**. *The health benefit of smoking cessation. A report of the Surgeon General.* Washington: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990.

9 **Halpern MT**, Gillespie BW, Warner KE. Patterns of absolute risk of lung cancer in former smokers. *J Natl Cancer Inst* 1993;**85**:457–64.

10 **Fletcher C**, Peto R, Tinker CM, *et al. The natural history of chronic bronchitis and emphysema.* Oxford: Oxford University Press, 1976.

11 **Scanlon PD**, Connett JE, Waller LA, *et al.* Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease: The Lung Health Study. *Am J Respir Crit Care Med* 2000;**161**:381–90.

12 **Kanner RE**, Connett JE, Williams DE, *et al.* Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: The Lung Health Study. *Am J Med* 1999;**106**:410–6.

13 **Burge PS**, Calverley PM, Jones PW, *et al.* Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;**320**:1297–303.

14 **Wright JL**, Lawson LM, Paré PD, *et al.* Morphology of peripheral airways in current smokers and ex-smokers. *Am Rev Respir Dis* 1983;**127**:474–7.

15 **Turato G**, Di Stefano A, Maestrelli P, *et al.* Effect of smoking cessation on airway inflammation in chronic bronchitis. *Am J Respir Crit Care Med* 1995;**152**:1262–7.

16 **Rutgers SR**, Postma DS, ten Hacken NHT, *et al.* Ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax* 2000;**55**:12–18.

17 **Vestbo J**, Sorensen T, Lange P, *et al.* Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;**353**:1819–23.

18 **Pauwels RA**, Löfdahl C-G, Laitinen LA, *et al.* Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999;**340**:1948–53.

19 **The Lung Health Study Research Group**. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:1902–9.

20 **Peto R**, Speizer FE, Cochrane AL, *et al.* The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. *Am Rev Respir Dis* 1983;**128**:491–500.

21 **Mannino DM**, Gagnon RC, Petty TL, *et al.* Obstructive lung disease and low lung function in adults in the United States. *Arch Intern Med* 2000;**160**:1683–9.

22 **Doll R**, Peto R, Wheatley K, *et al.* Mortality in relation to smoking: 40 years' observation on male British doctors. *BMJ* 1994;**309**:901–11.

23 **Pelkonen M**, Tukiainen H, Tervahauta M, *et al.* Pulmonary function, smoking cessation and 30 year mortality in middle aged Finnish men. *Thorax* 2000;**55**:746–50.

24 **Anthonisen NR**. Smoking, lung function, and mortality. *Thorax* 2000;**55**:729–30.

25 **Ashley F**, Kannel WB, Sorlie PD, *et al.* Pulmonary function: relation to aging, cigarette habit and mortality. The Framingham Study. *Ann Intern Med* 1975;**82**:739–45.

26 **Neas LM**, Schwartz J. Pulmonary function levels as predictors of mortality in a national sample of US adults. *Am J Epidemiol* 1998;**147**:1011–8.

27 **Soriano JB**, Maier WC, Egger P, *et al.* Recent trends in physician diagnosed COPD in women and men in the UK. *Thorax* 2000;**55**:789–94.

28 **Tashkin DP, Kanner R, Bailey W,** *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001;**357**:1571–5.

29 **Escobedo LG**, Peddicord JP. Smoking prevalence in US birth cohorts: the influence of gender and education. *Am J Public Health* 1996;**86**:231–6.

30 **Marks GB**, Burney PGJ. Diseases of the respiratory system. In: Charlton J, Murphy M, eds. *The health of adult Britain: 1841–1994.* Volume II. London: Stationery Office, 1997: 93–113.

31 **Doll R**, Darby S, Whitley E. Trends in mortality from smoking-related diseases. In: Charlton J, Murphy M, eds. *The health of adult Britain: 1841–1994.* Volume I. London: Stationery Office, 1997: 128–55.

32 **Peto R**, Lopez AD, Boreham J, *et al. Mortality from smoking in developed countries, 1950–2000.* Oxford: Oxford University Press, 1994.

33 **Whittemore AS**, Perlin SA, DiCiccio Y. Chronic obstructive pulmonary disease in lifelong nonsmokers: results from NHANES. *Am J Public Health* 1995;**85**:702–6.